45. (amended) The assay according to claim 42, wherein the probe contains a nucleic acid complementary to at least a portion of one or more HPV types selected from the group consisting of HPV types 6, 11, 33, 42, 43, 44, 16, 18, 31 and 35.

REMARKS

Applicants respectfully requests favorable reconsideration in view of the herewith presented amendment and remarks. The amended claims do not introduce new subject matter, nor do the amendments raise new issues of patentability. Entry of this amendment is respectfully requested. It is believed that entry of the amendment places the application into condition for allowance. If the Examiner decides to maintain the rejection of this application, entry of the amendment will reduce the number of issues remaining for appeal.

Claims 33-49 are pending in the instant application.

Claims 33-49 have been rejected under the judicially created obviousness-type double patenting. Applicants respectfully disagree with this rejection. However, in order to expedite the prosecution of the instant application, applicants submit herewith a newly executed terminal disclaimer.

The Examiner correctly noted that the previously filed terminal disclaimer was directed to the wrong patent. Therefore, applicants withdraw the previously filed terminal disclaimer directed to USP 5,981,179. The newly executed terminal disclaimer is correctly directed to US Patent 6,228,578. Entry of this terminal disclaimer is respectfully requested. Reconsideration and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

Claim 33 has been rejected under 35 U.S.C. §112, first paragraph. The Examiner asserts that the phrase "unmodified probe" is not supported in the originally filed specification and "there is no art recognized definition for what constitutes and unmodified probe." Applicants respectfully disagree with this rejection.

Applicants have amended the claims to address the Examiner's concerns. The term "unmodified nucleic acid probe" refers to a nucleic acid, which is not chemically or structurally changed from what is understood in the art to be a nucleic acid, and which is being used as a probe. As the Examiner is undoubtedly aware, a specification need not be burdened with subject matter well-known in the art. The skilled artisan is fully aware of modifications which render a nucleic acid detectable and those which render the nucleic acid attachable or attached to a solid matrix. These are modifications which are not necessary with the present invention and the skillled artisan would recognize this feature of the invention reading its description in the specification. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 33 and 43-45 have been rejected under 35 U.S.C. §112, second paragraph. Applicants respectfully disagree with this rejection.

In particular, claim 33 has been rejected under §112, second paragraph as being indefinite for the recitation of the term "unmodified" probes. The Examiner argues that "there is no art recognized definition for what constitutes an unmodified probe." For the reasons discussed above, applicants respectfully disagree with this position. "Unmodified nucleic acid probes" are understood in the art to be probes which comprise nucleic acids which are chemically and structurally unmodified from that which is understood to be a nucleic acid. Nucleic acids have a structure which occurs in nature and can be duplicated synthetically or

recombinantly. This structure constitutes a nucleic acid. A skilled artisan, looking at a nucleic acid structure can immediately recognize nucleic acids which are unmodified as compared to those whose structure has been modified and contain an altered chemistry and/or structure. Modifications necessary for detection or attachment to a solid matrix are clearly modifications not necessary for the present invention, because the probes of the present invention are neither attached to a matrix nor detectably labeled. For these reasons, applicants believe that the phrase "unmodified nucleic acid probes", as amended, is not indefinite. Reconsideration and withdrawal of this §112 rejection is respectfully requested.

Claims 43-45 have been rejected under 35 U.S.C. §112, second paragraph for the phrases "probe comprises HPV 6 and HPV 11", "probe comprises HPV 16", and "probe contains one or more HPV types" because these phrases are unclear. Applicants respectfully disagree with this rejection. However, in order to facilitate prosecution of the instant application, applicants have amended the claims to address the Examiner's concerns. Reconsideration and withdrawal of this §112 rejection is respectfully requested.

Claim 33 has been rejected under 35 U.S.C. §103(a) as being obvious over Rashtchian. Applicants respectfully disagree with this rejection.

Rashtchian describe the use of a biotinylated probe and a streptavidin conjugated peroxidase to detect the complex. The reference provides no teaching or suggestion on how the assay could be carried out with an unmodified probe, nor does the reference provide any motivation to change the format of the assay. One skilled in the art would not be motivated to construct a kit meeting the limitations of the instant claims based upon Rashtchian, because there is no deficiency with the use of a biotinylated probe as described in the Rashtchian assay. There is no teaching or suggestion in the Rashtchian reference to modify the probe to be unmodified.

The Examiner argues that because the term "unmodified" is considered to be indefinite, the biotinylated probe of Rashtchian's assay is believed to be included in the claim. Any skilled artisan would recognize that a biotin attached to a nucleic acid is a modification of the chemical and structural integrity of a nucleic acid. Thus, the nucleic acid probe of Rashtchian is clearly NOT an unmodified nucleic acid probe, as defined above and as is known in the art. Therefore, applicants respectfully request reconsideration and withdrawal of this §103(a) rejection.

Claims 33-36 have been rejected under 35 U.S.C. §103(a) as obvious over Rashtchian in view of Carrico. Applicants respectfully disagree with this rejection.

As discussed above, Rashtchian describes an assay which uses a biotinylated probe, which according to a common understanding of the term "modified" is considered a modified nucleic acid probe. This is because the biotinylation alters the chemical and structural integrity of the nucleic acid.

Similarly, Carrico uses modified probe, in that the probe described in this assay must be physically immobilized or immobilized onto a solid matrix so that the test nucleic acid can be separated from the sample. *See, e.g.*, col. 4, lns. 22-25, which states that the Carrico assay provides "the probe in preferred embodiments in an already immobilized form or in a form which is readily immobilized by binding to an immobilized binding partner". *See also*, Carrico, Figures 1 and 2 and all of the Examples. Carrico specifically points out the benefits of using an immobilized probe. *See, e.g.*, Carrico, col. 3, lns. 54-61.

Combining the teachings of Rashtchian with Carrico does not lead to the invention as claimed. Rashtchian detects the complex directly from a labeled probe, while Carrico immobilizes the complex using a immobilized or immobilizable probe. Neither

Rashtchian nor Carrico teaches or suggests that a completely unmodified probe can be used in an assay, which both immobilizes and detects a target complex. Neither of these references teaches or suggests how the skilled artisan could accomplish both of these critical steps without first modifying the probe used in the assay. Also, neither Rashtchian or Carrico teach or suggest that the assay can use an antibody to both capture and detect the DNA-RNA complex. This alternation in the assay is not an intuitive change in view of these two references, in that the skilled artisan may well be concerned about antibody saturation of the hybrid at its first use and therefore, not use the antibody for two different steps in the assay.

Also, both the Rashtchian reference and Carrico reference emphasize the need to minimize the number of steps in their assays. Important to this end is the use of a modified probe; *i.e.*, labeled probe, in the case of Rashtchian, or an immobilized or immobilizable probe, in the case of Carrico. Neither of these references suggests adding a step or two to their assay systems to accomplish that which is done with the modified probe in a single step with a single reagent. The use of an antibody for both immobilization and detection adds steps to the assay system described by Rashtchian and Carrico. One skilled in the art would not be motivated to change the prior art assay systems to one which would add steps to the assay. This would be counter-intuitive and counter-productive, in the mind of a skilled artisan.

For all of the above reasons, applicants submit that the combination of Rashchian and Carrico do not teach or suggest the claimed invention and therefore, do not rendered claims 33-36 obvious. Thus, applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Claims 37-40 have been rejected under 35 U.S.C. §103(a) as being obvious over Rashtchian in view of Carrico and further in view of Thompson. Applicants respectfully disagree with this rejection.

As discussed above, applicants maintain that the independent claims are not rendered obvious over Rashtchian in view of Carrico, because neither Rashtchian nor Carrico teach or suggest the use of an unmodified probe or the use of an antibody for two separate steps in the assay. As discussed above, these are not trivial changes. Modification of the probe in Rashtchian is critical for detection of the complex, while modification of the probe in Carrico is critical for immobilization of the complex. Neither reference alone or read in combination teaches or suggests that both of these steps can instead use an antibody to the complex. In fact, both of these references discuss the advantages of using either the labeled probe or the immobilizable probe as a way to reduce the number of reagents and steps in the assay method. Thus, neither reference provides motivation to modify the assay to use an antibody in two separate steps, thereby adding steps to the assay system. As discussed above, this modification of the references may well be avoided by the skilled artisan who may be concerned about antibody saturation of the hybrid. For these reasons, applicants believe that the independent claims are not rendered obvious over Rashtchian in view of Carrico.

Thompson was cited by the Examiner for its description of the use of an RNase to eliminate excess probe. Also, the Examiner relies on a general statement about target saturation with probe to conclude that the claimed concentrations of probe are obvious. However, the Thompson reference does not remedy the deficiencies of the Rashtchian and Carrico primary references, in that Thompson also does not teach or suggest the use of an antibody for two separate steps in the assay. Thompson merely describes the use of ribonuclease to digest

unreacted probe. The Examiner's reliance on Thompson for a teaching of probe concentration is inappropriate, because the reference does not teach or suggest that the claimed probe concentrations could be used. Without some additional teaching or suggestion as to the steps and elements of the claims, Thompson does not add to the cited prior art to render the claimed invention obvious. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

Claims 41, 42, 46, 47, 48 and 49 have been rejected under 35 U.S.C. §103(a) as being obvious over Rashtchian in view of Carrico and further in view of Longiaru. Applicants respectfully disagree with this rejection.

As discussed above, applicants assert that Rashtchian in view of Carrico does not teach or suggest an assay which uses an antibody in two separate steps of the assay and its use as a reagent in two separate assay steps is not encouraged in the art due to saturation properties of antibody binding sites. Longiaru does not address this problem in the art and therefore does not remedy the deficiencies of the primary references. Longiaru describes a PCR-based assay for the detection of microorganisms. It does not teach or suggest the use of an antibody in two separate steps of an RNA-DNA hybrid detection system. Therefore, applicants assert that Rashtchian in view of Carrico and further in view of Longiaru do not teach or suggests all of the elements or steps of the claims and thus, do not render claims 41, 42, 46, 47, 48 and 49 obvious. Reconsideration and withdrawal of this §103 rejection is respectfully requested.

Claims 41-45 and 47 have been rejected under 35 U.S.C. §103(a) as obvious over Rashtchian in view of Carrico and further in view of Herzog. Applicants respectfully disagree with this rejection.

Herzog describes various HPV probes. The reference does not teach or suggest the use of an antibody for two separate steps in the assay. Nothing in this reference teaches or suggest that it is desirable to add steps to the methods of Rashtchian and/or Carrico. Thus, one skilled in the art would not be motivated to modify the assay of Rashtchian or Carrico to include additional steps, in view of the fact that the particular advantage in both of these references is the use of a modified probe, i.e. labeled for detection in Rashtchian, immobilized or immobilizable in Carrico, in order to reduce the number of steps in the assay system. Herzog does not add to these references to reach the basic steps of the instant claimed invention. Therefore, Rashtchian in view of Carrico, in view of Herzog does not render claims 41-45 and 47 obvious. Applicants respectfully request reconsideration and withdrawal of this rejection.

Allowance of the pending claims is respectfully requested. Early and favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

No additional fee is believed to be necessary.

The Commissioner is hereby authorized to charge any additional fees which may be required for this amendment, or credit any overpayment to Deposit Account No. 13-4500, Order No. 2629-4023.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for

an extension of time to Deposit Account No. 13-4500, Order No. 2629-4023. A DUPLICATE OF THIS SHEET IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: Aug 16, 2002

By: Dorothy R. Auth
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VERSION WITH MARKINGS SHOWING CHANGES

33. (amended) A solution hybridization kit for the detection of a target nucleic acid sequence for diagnosing genetic defects, microbial or viral infections in a biological sample with an accuracy of at least 89% comprising:

a) a sample transport medium for stabilization of the biological sample;

b) an unmodified nucleic acid probe complementary to the target nucleic acid sequence for formation of a double-stranded RNA/DNA hybrid;

c) a solid phase to which an anti-hybrid antibody or a functional anti-hybrid antibody fragment has been immobilized, wherein the antibody or antibody fragment specifically binds to a component of the double-stranded RNA/DNA hybrid; and

d) means for detecting the hybrid formed by hybridization of the probe and the target nucleic acid sequence.

42. (amended) [The assay according claim 41] A non-radioactive hybridization assay for the detection of a target human papilloma virus (HPV) nucleic acid sequence in a biological sample suspected of containing the virus, comprising the steps of:

a) hybridizing the target HPV nucleic acid to a complementary nucleic acid probe to form a double-stranded RNA:DNA hybrid;

b) capturing the hybrid onto a solid phase to which an anti-hybrid antibody or functional anti-hybrid antibody fragment has been immobilized, wherein the antibody or antibody fragment specifically binds to a component of the double-stranded RNA:DNA hybrid forming a bound hybrid;

c) eliminating any non-hybridized probe; and

d) binding an antibody reactive with a RNA:DNA hybrid to the bound hybrid forming an antibody bound hybrid, thereby detecting the viral nucleic acid sequence., [wherein the target viral nucleic acid sequence is from human papilloma virus (HPV).]

43. (amended) The assay according to claim 42, wherein the probe comprises a nucleic acid complementary to at least a portion of HPV 6 and HPV 11.

44. (amended) The assay according to claim 42, wherein the probe comprises a nucleic acid complementary to at least a portion of HPV 16, HPV 18, HPV 31, HPV 33 and HPV 35.

45. (amended) The assay according to claim 42, wherein the probe contains a nucleic acid complementary to at least a portion of one or more HPV types selected from the group consisting of HPV types 6, 11, 33, 42, 43, 44, 16, 18, 31 and 35.